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(54) Pro-drugs of 5-(2-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)ethyl)-6-chloro-1,3-dihydro-2h-indol-2-one

(57) The present invention relates to a pro-drug of ziprasidone or pharmaceutically acceptable salts thereof, processes for its preparation, and pharmaceutical compositions and methods of treatment comprising said pro-drug.

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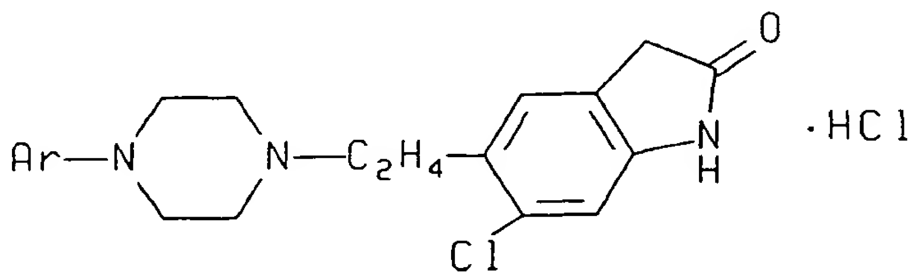
Description

Background of the Invention

The present invention relates to the compound 1-[2-(6-chloro-2,3-dihydro-2-oxo-1H-indol-5-yl)ethyl]-4-[imino(2-mercaptophenyl)methyl]piperazine or one of its pharmaceutically acceptable salts, to processes for its preparation, to pharmaceutical compositions and to methods of treatment. 1-[2-(6-Chloro-2,3-dihydro-2-oxo-1H-indol-5-yl)ethyl]-4-[imino(2-mercaptophenyl)methyl]piperazine is a pro-drug of 5-(2-(4-(1,2-benzisothizol-3-yl)-1-piperazinyl)ethyl)-6-chloro-1,3-dihydro-2H-indol-2-one (hereinafter referred to as ziprasidone). The compound of the invention, 1-[2-(6-chloro-2,3-dihydro-2-oxo-1H-indol-5-yl)ethyl]-4-[imino(2-mercaptophenyl)methyl] piperazine, has neuroleptic activity and is therefore useful as an antipsychotic.

The aqueous solubility of the dihydrochloride salt of 1-[2-(6-chloro-2,3-dihydro-2-oxo-1H-indol-5-yl)ethyl]-4-[imino(2-mercaptophenyl)methyl]piperazine at about 25°C is about 25 mg/mL which is approximately 300 times higher than ziprasidone hydrochloride (8.0 μg/mL).

U.S. Patent No. 4,831,031, issued May 16, 1989, which is hereby incorporated by reference in its entirety, discloses 5-(2-(4-(1,2-benzisothizol-3-yl)-piperazinyl)ethyl)-6-chloro-1,3-dihydro-2H-indol-2-one hydrochloride, which has the formula



wherein Ar is benzisothiazol-3-yl, in the hemihydrate form (hereafter "the hemihydrate").

United States Patent 5,312,925 issued May 17, 1994, which is hereby incorporated by reference in its entirety, refers to the monohydrate hydrochloride salt of ziprasidone, processes for its preparation, and pharmaceutical compositions and methods of treating psychotic disorders.

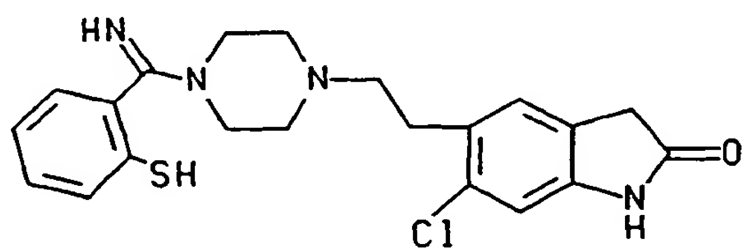
United States Patent 5,359,068, issued October 25, 1994, which is hereby incorporated by reference in its entirety, refers to processes and intermediates for the preparation of ziprasidone.

United States Patent 5,206,366, issued April 27, 1993, which is hereby incorporated by reference in its entirety, refers to an aqueous based process for preparing ziprasidone.

United States Patent Application 60/006,301, filed November 7, 1995, refers to the preparation of 1-(1,2-benziso-thiazol-3-yl)piperazine which is a key intermediate in the preparation of ziprasidone.

Summary of the Invention

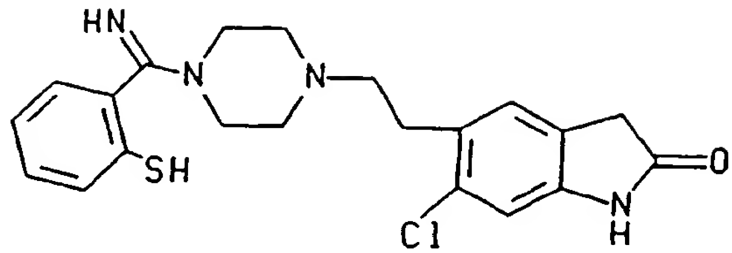
The present invention relates to a compound of the formula



I

or pharmaceutically acceptable salts thereof.

The present invention also relates to a process for preparing a compound of the formula



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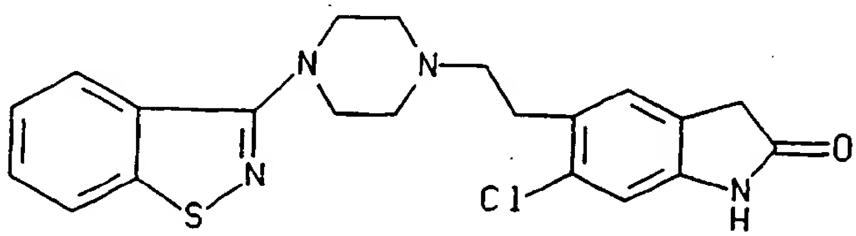
comprising reacting a compound of the formula



II

with a reducing agent. Preferably, the reducing agent is benzyl mercaptan (more preferably 2.2 equivalents of benzyl mercaptan relative to the amount of ziprasidone). In a more preferred embodiment of the invention, a solvent is added to facilitate the reaction. Preferably the solvent is isopropanol. Most preferably, the reaction is run at about 85°C for about 6 hours.

This invention also relates to a pharmaceutical composition having neuroleptic activity comprising, the compound of formula I in an amount effective in the treatment of neuroleptic diseases, and a pharmaceutically acceptable carrier.

This invention also relates to a method of treating neuroleptic diseases which comprises, administering to a subject in need of treatment a neuroleptic amount of a compound of formula I.

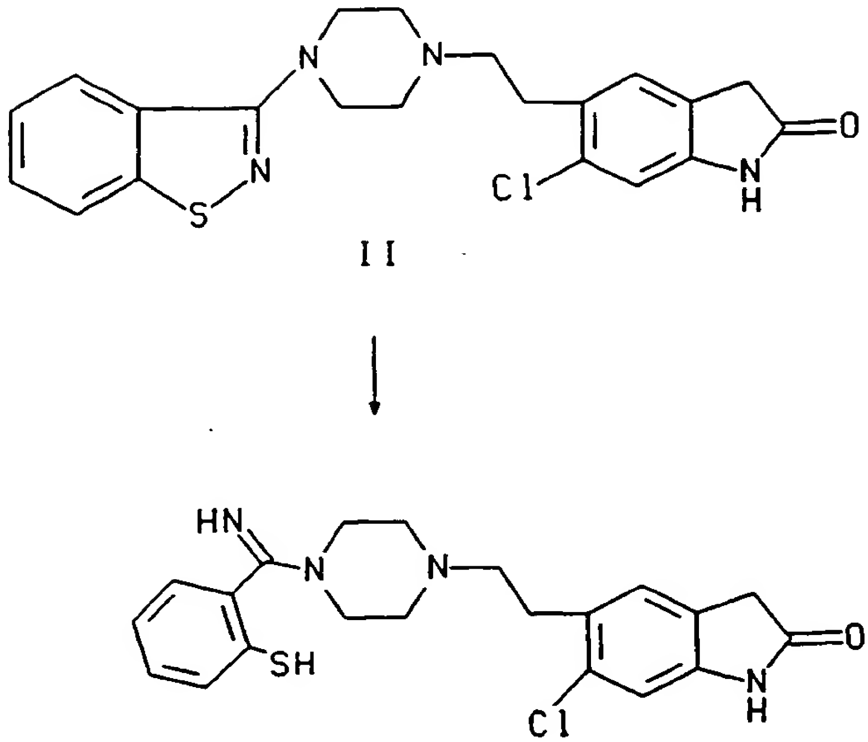
Bisulfite when used herein refers to sodium bisulfite ($NaHSO_3$) or potassium bisulfite ($KHSO_3$).

Metabisulfite when used herein refers to sodium metabisulfite ($Na_2S_2O_5$) or potassium metabisulfite ($Na_2S_2O_5$).

Detailed Description

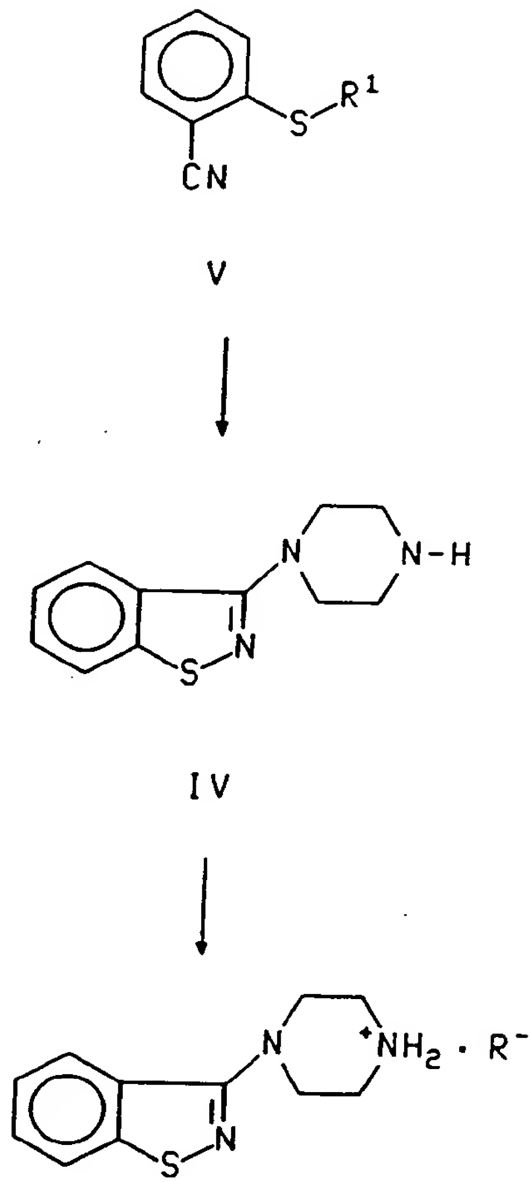
The compounds of the formula I and ziprasidone can be prepared as described in the following reaction Schemes and discussion. Unless otherwise indicated, compounds of the formulae I and II in the reaction Schemes and discussion are as defined above.

SCHEME 1



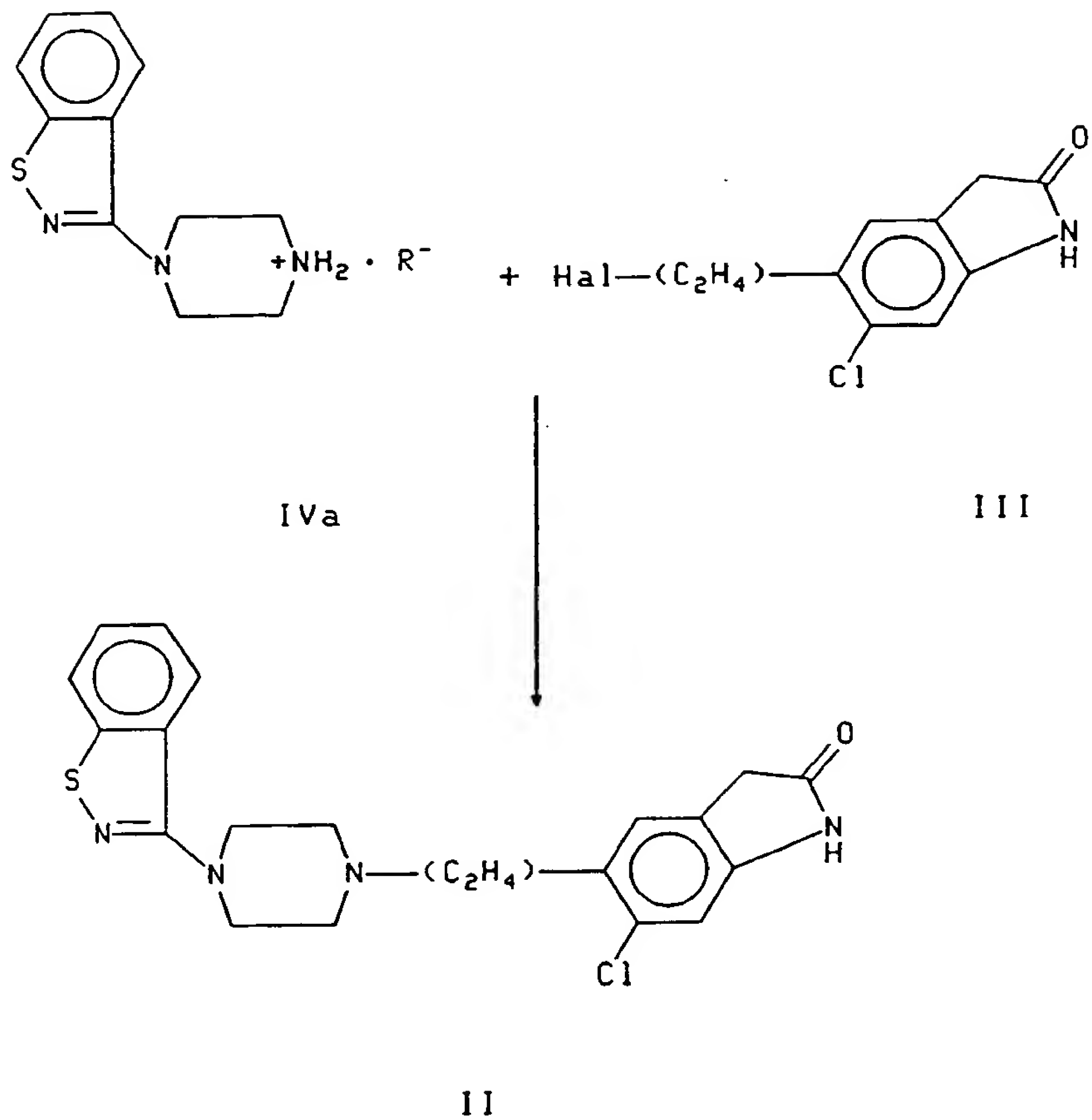
I

SCHEME 2



IVa

SCHEME 3

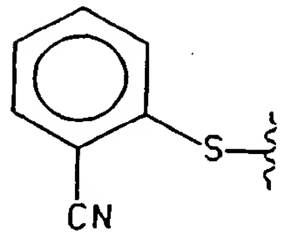


Scheme 1 refers to the preparation of 1-[2-(6-chloro-2,3-dihydro-2-oxo-1H-indol-5-yl)ethyl]-4-[imino(2-mercaptophenyl)methyl]piperazine from ziprasidone. Ziprasidone can be prepared according to the procedures of Schemes 2 and 3 as well as by other methods described below.

Referring to Scheme 1, ziprasidone is treated with a reducing agent at a temperature from about 50°C to about 150°C, preferably about 85°C, for about 3 to about 10 hours, preferably about 6 hours. Suitable reducing agents include benzyl mercaptan, lower alkyl mercaptans (such as t-butyl mercaptan, methyl mercaptan, butylmercaptan), bisulfites and metabisulfites. Preferably the reducing agent is benzyl mercaptan. The reducing agent preferably comprises about 1 to about 4 equivalents (relative to the amount of ziprasidone) preferably about 2.2 equivalents. Preferably a solvent is added to facilitate the reaction. Suitable solvents include alcohols (such as isopropanol, t-butanol, methanol or ethanol), or tetrahydrofuran, preferably isopropanol. The solvent is preferably about 5 to about 15 volumes (relative to the weight of ziprasidone). Most preferably, the solvent is about 10 volumes (relative to the weight of ziprasidone).

Scheme 2 refers to the preparation of intermediates of the formula IV which are useful in the synthesis of ziprasidone, as described in United States Patent Application, 60/006,301 filed November 7, 1995. These intermediates of the formula IV or IVa which can be converted into ziprasidone, by the methods of Scheme 3.

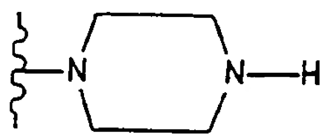
Referring to Scheme 2, a compound of the formula V, wherein R^1 is



c

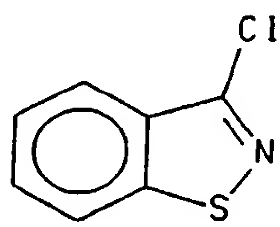
is commercially available or can be prepared according to the method of Japanese Patent Publication 6,220,030, published August 9, 1994.

A compound of the formula V wherein R^1 is



a

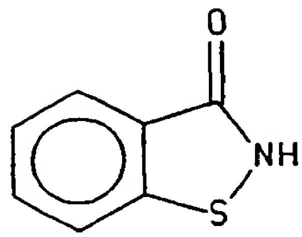
may be prepared by reacting a compound of the formula



VI

with about 1 to about 10 equivalents of piperazine, preferably about 2 to about 5 equivalents of piperazine is used. The temperature of the aforesaid reaction is between about 25°C to about 105°C, preferably about 65°C. The reaction time varies from about 1 hour to about 20 hours, preferably from about 2 to about 6 hours.

The compound of formula VI is prepared from an amide of the formula

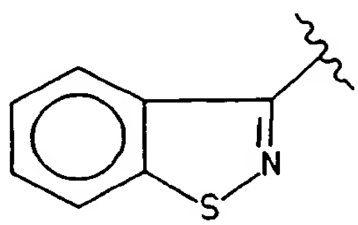


VII

by reaction with about 1 to about 3 equivalents of a chlorinating agent such as phosphorous oxychloride ($POCl_3$), phosphorous trichloride (PCl_3), or phosphorous pentachloride (PCl_5) in reaction inert solvent. Preferably about 1.2 equivalents of phosphorous oxychloride is used as the chlorinating agent. Suitable solvents include dimethylformamide, dimethylacetamide, or pyridine, preferably dimethylformamide. The reaction time of the aforesaid reaction is from about 1 to about 5 hours, preferably about 3.5 hours. The reaction is performed at a temperature from about 30°C to about 100°C, preferably about 70°C.

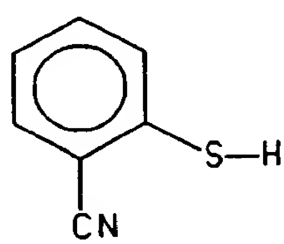
The compound of the formula VII is commercially available.

Compounds of the formula V, wherein R^1 is



b

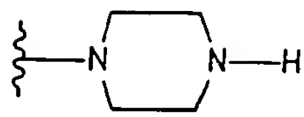
can be prepared by reacting bis(2-cyanophenyl)disulfide with a compound of the formula



VIII

in a reaction inert solvent. Suitable reaction inert solvents include isopropanol, ethanol, or tetrahydrofuran, preferably isopropanol. The temperature of the aforesaid reaction is about 50 °C to about 120 °C. The reaction time of the aforesaid reaction is about 1 hour to about 3 hours, preferably about 2 hours.

A compound of the formula V, wherein R^1 is



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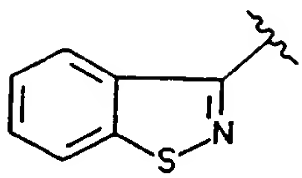

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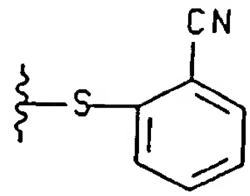
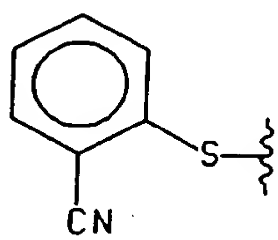


b c

can be converted into a compound of the formula IV by reaction with from about 2 to about 20 equivalents of piperazine (preferably anhydrous). The preferred amount of piperazine is the amount of piperazine that minimizes bis substitution of the free amine of the piperazine group of the compound of the formula IV. The preferred R^1 is



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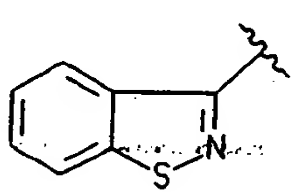
c

When R^1 is a group of the formula "c", as depicted above, the preferred amount of piperazine is about 5 to 10 equivalents, most preferably about 10 equivalents. The temperature of the aforesaid reaction is between about 76°C and 200°C, preferably about 120°C. The reaction time varies depending on the temperature at which the reaction is run. As the reaction temperature is increased the reaction time is decreased. When the reaction is run at about 80°C, only small amounts of product are formed after 2 days. When the reaction is run at about 200°C, the vessel must be pressurized to prevent loss of the piperazine and the clearing agent and the ensuing reaction time is about 1 hour. When the reaction is performed at high temperatures, the internal reaction vessel pressure is between about 50 to 60 psi and as such is well within the standard pressure capacities for commercial reactors. When the reaction is performed at the ideal temperature of about 120°C the reaction time is about 24 hours.

The reaction between a compound of the formula V, wherein R^1 is



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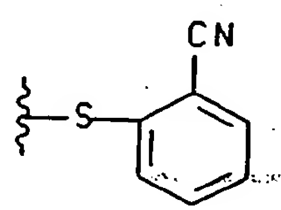
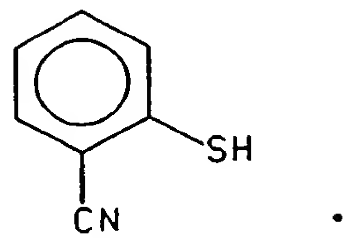


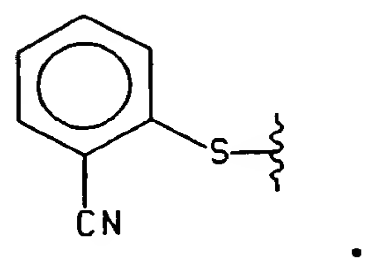
b c

, and piperazine generates a thiol by-product of the formula



VIII

A preferred embodiment of the reaction involves the in situ oxidation of the compound of formula VIII into a compound of the formula V, wherein R^1 is



C

This in situ oxidation is facilitated by adding from about 1 to about 10 equivalents, preferably 4 equivalents, of an oxidant to the reaction vessel. Suitable oxidants include dimethyl sulfoxide, air, copper (II) salts, bisulfite, metabisulfite or hydrogen peroxide, preferably dimethyl sulfoxide. When dimethyl sulfoxide is the oxidant, preferably about 2 to 5 equivalents are used in the reaction.

In another preferred embodiment of the reaction about 0.5 to about 5 volumes of a piperazine clearing agent is added to the reaction vessel so as to prevent piperazine from solidifying in the head space and vapor lines of the reaction vessel. Suitable piperazine clearing agents have boiling points in the range of about 70°C to about 130°C, such as isopropanol or t-butanol, pyridine, toluene or diglyme, preferably isopropanol. Preferably about 1.2 volumes (a relative proportion (mL/gm) to the weight of the compound of formula II) of the piperazine clearing agent is used.

A compound of the formula IV can be converted to the more stable pharmaceutically acceptable salts of the formula IVa, wherein R is a pharmaceutically acceptable anion conjugate of a pharmaceutically acceptable acid, by treatment of the free base of formula IV with a pharmaceutically acceptable acid of the formula RH in a polar solvent. Suitable acids of the formula RH are those which form non-toxic acid addition salts, e.g., salts containing pharmacologically acceptable anions, such as chloride, bromide, iodide, nitrate, sulfate or bisulfate, phosphate or acid phosphate, acetate, lactate, citrate or acid citrate, tartrate or bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts. Preferably the acid is hydrochloric acid. Suitable solvents include lower alcohols, such as methanol, ethanol, isopropanol or t-butanol, toluene, ethers such as diethyl ether or tetrahydrofuran, or mixtures of the above solvents. Preferably the solvent is a mixture of isopropanol and toluene.

The conversion of the compound of formulae IV or IVa to ziprasidone follows the processes described in United States Patents 4,831,031, 5,206,368 or 5,359,068 ; which issued on May 16, 1989, April 27, 1993 and October 25, 1994 respectively.

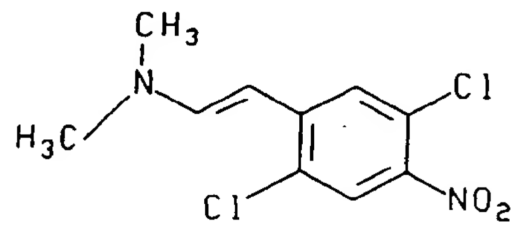
Scheme 2 refers to the preparation of ziprasidone from compounds of the formula IV or IVa according to the processes described in United States Patent 4,831,031, issued May 16, 1989. Specifically, a compound of the formula IV or IVa is reacted with a compound of the formula III wherein Hal is fluoro, chloro, bromo or iodo. This coupling reaction is generally conducted in a polar solvent such as a lower alcohol, for instance ethanol, dimethylformamide or methyl isobutyl ketone, and in the presence of a weak base such as a tertiary amine base, for instance triethylamine or diisopro-

pylethylamine. Preferably, the reaction is performed in the further presence of a catalytic amount of sodium iodide, and a neutralizing agent for hydrochloride such as sodium carbonate. The reaction is preferably conducted at the reflux temperature of the solvent used.

Alternatively, Scheme 2 also refers to the conversion of compounds of formula IV or IVa into ziprasidone by the methods of United States Patent 5,206,366, issued April 27, 1993. Specifically, a compound of formula IV or IVa is reacted with a compound of formula III, wherein Hal is fluoro, chloro, bromo or iodo. This coupling reaction is conducted in refluxing water with a hydrohalic acid neutralizer.

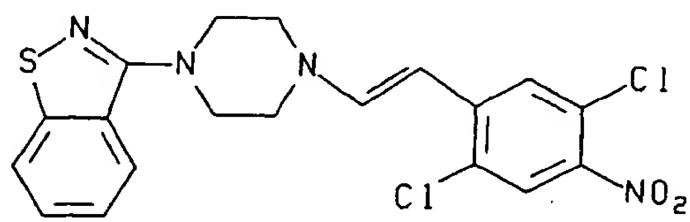
Alternatively, compounds of the formula IV can be converted to ziprasidone by the methods described in United States Patent 5,359,068, issued October 25, 1994.

Specifically, compounds of the formula I may be reacted with a compound of the formula



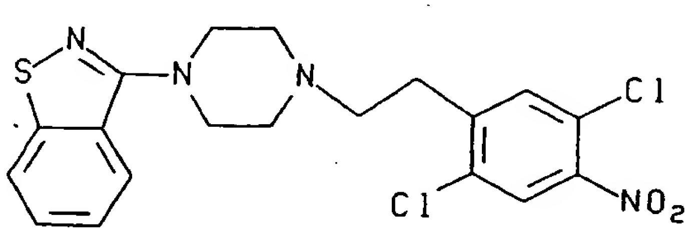
IX

in the presence of a (C_1-C_6) alkanoic acid to form the compound of the formula



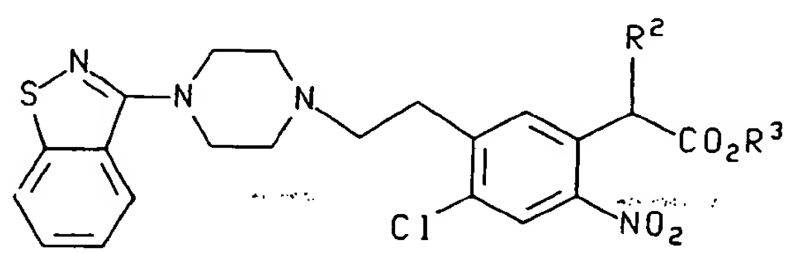
X

The compound of the formula X can then be treated with a reducing agent to form the compound of the formula



XI.

The compound of the formula XI can then be treated with a compound of the formula R^2-CH_2-CO_2R^3 wherein R^2 is CO_2R^3 or CN and R^3 is (C_1-C_6)alkyl to form a compound of formula



XII

,wherein R^2 is CN or CO_2R^3 and R^3 is (C_1-C_6)alkyl.

The compound of formula XII can then be treated with an acid at an elevated temperature to form the compound of formula XII wherein R^2 and R^3 are both hydrogen.

The compound of formula XII can then be treated with a (C_1-C_6)alkanol in the presence of an acidic esterification catalyst to form the compound of formula XII wherein R^2 is hydrogen and R^3 is (C_1-C_6)alkyl.

The compound of the formula XII, wherein R^2 is hydrogen, CN or CO_2R^3 and R^3 is hydrogen or (C_1-C_6)alkyl, can then be treated with a reducing agent with the proviso that when R^2 is CN or CO_2R^3 and R^3 is (C_1-C_6)alkyl the product of the reduction is heated with an acid to form ziprasidone.

Specific details of the reaction steps of converting compounds of the formula IV into ziprasidone can be found in United States Patent 5,359,068, issued October 25, 1994.

The compound of formula I possesses potent neuroleptic activity. The compound of formula I is therefore useful in the treatment or prevention of psychotic disorders, such as schizophrenia. The neuroleptic activity of the compound of the invention may be demonstrated by methods well known to those of ordinary skill in the art, such as the methods described in T.F. Seeger, et al., Journal of Pharmacology and Experimental Theraputics, 275, (1), 101-113 (1995). Specifically, the standard methods for determining neuroleptic activity are based on Dopamine D-2, Dopamine D-3, Dopamine D-4, 5-hydroxytryptamine-1A (5-HT-1A), 5-hydroxytryptamine-2C (5-HT-2C), and 5-hydroxytryptamine-2A (5-HT-2A) receptor binding studies. Tissues or membranes used to perform these studies are derived from rat, pig, or from cell lines expressing human receptor subtypes. LTK-cells expressing the human $D2_{Long}$ receptor were obtained from Dr. Olivier Civelli, Oregon Health Sciences University, Portland, Oregon. Chinese hamster ovary cells (CHO) expressing the human D3 receptor were obtained from Dr. J.C. Schwartz, Unite de Neurobiologie, Institut National de la Sante' et de la Recherche Medicale, 2 ter Rue D'Ale' Sia, Paris, France, 75014.

The following protocol describes one possible method for determining activity for the compound of formula I. Specific assay conditions for each receptor is described in Table 1, below. Tissues or cell lines of interest are homogenized in various buffer solutions (details are given in Table 1) using a Brinkman Polytron at setting 6 for 20 sec. Membranes are recovered after multiple rounds of separation by centrifugation and resuspension in fresh ice-cold buffer. The resulting tissue homogenates are added to test tubes containing incubation buffer, various concentrations of test drug, and the appropriate tritiated or iodinated ligand. Non-specific binding is determined by radioligand binding in the presence of a saturating excess of a known competitor for the receptor of interest (as listed in Table 1). After allowing sufficient time to attain equilibrium at the appropriate temperature, incubations are terminated by rapid filtration through Whatman GF/B filters using a Brandel cell harvester. The membranes are washed three times with four ml aliquots of ice-cold buffer. Membrane-bound ligand is determined by liquid scintillation counting of the filters in Ready-Safe scintillation cocktail (for tritiated ligands), or by direct counting in a gamma counter (for $[^{125}I]$ ligands). For all receptor types, the dissociation constant (K_d) for the radioligand is previously determined by saturation analysis in the tissue of interest, and used to calculate apparent K_i's by means of the Cheng-Prusoff equation (Cheng and Prusoff, 1973). In some cases the IC_{50} concentration (concentration of compound required to displace specific binding by 50%) can be interpolated by linear regression analysis of the concentration-response curves from competition binding studies.

The compound of the invention possessed the receptor binding results depicted in Table 2

TABLE 1

Assay Conditions for Radioligand Binding Studies				
Receptor	Ligand concentration	Tissue	Blank	Buffer pH
Dopamine D-2	3H-spiroperidol .2 nM + 1 μM prazosin + 500 nM cinanserin	rat caudate	(+)-butaclamol 5 μM	50 mM TrisHCl, 100 mM NaCl, 1 mM $MgCl_2$, pH 7.2
Dopamine D-3	3H-spiroperidol 0.1 nM	human D3-transfected CHO cells	(+)-butaclamol 2 μM	50 mM TrisHCl pH 7.4, 120 mM NaCl, 5 mM KCl, 2 mM MgCl2, 2 mM $CaCl_2$
Dopamine D-4	3H-spiroperidol 0.1 nM	human D4-transfected COS-7 cells	(+)-butaclamol 2 μM	50 mM TrisHCl pH 7.4, 120 mM NaCl, 5 mM KCl, 2 mM $MgCl_2$, 2 mM $CaCl_2$
5HT-1A	3H-80H-DPAT 1.5 nM	rat cortex	serotonin 10 μM	50 mM TrisHCl, 0.1% ascorbate, 4 mM $CaCl_2$ 10 μM pargyline pH 7.7
5HT-2C[10]	3H-mesulergine 1 nM	pig choroid plexus	serotonin 10 μM	50 mM TrisHCl, 0.1% ascorbate 4 mM $CaCl_2$ pH 7.7
5HT-2A	3H-ketanserin .4 nM + 1μM prazosin + 500 nM mepyramine	rat frontal cortex	methysergide 2 μM	50 mM TrisHCl ph 7.7

TABLE 2

Receptor	Radioligand Binding Results
D2	2.3 nM
D3	5.8 nM
D4	59.2 nM
5HT2	0.35 nM (IC_{50})
5HT1A	12 nM(IC_{50})

Pro-drugs of ziprasidone may be administered as a neuroleptic agent. Administration to a human subject may be alone or, preferably, in combination with pharmaceutically acceptable carriers or diluents in a pharmaceutical composition, in accordance with standard pharmaceutical practice. The pro-rugs of ziprasidone may be administered orally or parenterally including intravenously or intramuscularly. Suitable pharmaceutical carriers include solid diluents or fillers, and sterile aqueous solutions and various organic solvents. The pharmaceutical compositions are then readily administered in a variety of dosage forms, such as tablets, powders, lozenges, syrups, and injectable solutions. These pharmaceutical compositions, if desired, may contain additional ingredients such as flavorings, binders and excipients. Thus, for purposes of oral administration, tablets containing various excipients such as sodium citrate, calcium carbonate and calcium phosphate may be employed along with various disintegrants such as starch, alginic acid and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in soft and hard filled gelatin capsules. Preferred materials for this include lactose or milk sugar and high molecular weight polyethylene glycols. When aqueous suspen-

sions or elixirs are desired for oral administration, the essential active ingredient therein may be combined with various sweetening or flavoring agents, coloring matter or dyes and, if desired, emulsifying or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin and combinations thereof.

For parenteral administration, a solution or suspension of a pro-drug of ziprasidone in sesame or peanut oil, aqueous propylene glycol, or in sterile aqueous solution may be employed. Such aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. The sterile aqueous media employed are all readily available by standard techniques known to those skilled in the art.

The effective dosage for a pro-drug of ziprasidone depends on the intended route of administration and other factors such as age and weight of the subject, as generally known.

The following Examples illustrate the preparation of the pro-drugs of the present invention. Commercial reagents were utilized without further purification. Melting points are uncorrected. NMR data are reported in parts per million (δ) and are referenced to the deuterium lock signal from the sample solvent. Unless otherwise stated, all mass spectrum were performed using electron impact (EI, 70 eV) conditions. Unless otherwise indicated, chromatography refers to column chromatography performed using 32-63μm silica gel and executed under nitrogen pressure (flash chromatography) conditions. High Pressure Liquid Chromatography (HPLC) was performed on a LDC Analytical constaMetric® 3200 HPLC (Thermo Separation Products Co.). A Zorbax®C8, 60Å, 3.9 x 150 mm column (Mac-Mod Analytical, Inc., Chadds Ford, PA 19317) was used for HPLC analysis (mobile phase: 40% acetonitrile, 45% 0.05M potassium phosphate, monobasic (KH_2PO_4) adjusted to pH = 6.0 with potassium hydroxide (KOH), 15% methanol; Flow Rate of 1.0 ml/minute; Detector: UV 229 nm; Injector: 10 ul; Samples are prepared in mobile phase (0.05 mg/ml)). Room temperature refers to 20-25°C.

Example 1

1-[2-(6-Chloro-2,3-dihydro-2-oxo-1H-indol-5-yl)ethyl]-4-[imino(2-mercaptophenyl)methyl]piperazine

A one-liter, 3-neck round bottom flask equipped with a mechanical stirrer, condenser topped with a nitrogen inlet, and thermometer was purged and then maintained under an inert nitrogen atmosphere. 5-[2-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one (60.0 g, 145 mmol), 2-propanol (600 mL), and benzyl mercaptan (45.1 g, 363 mmol) were added to the flask affording a pink slurry which was heated to reflux (83°C). After 6 hours at reflux, thin layer chromatography (eluted with methylene chloride/isopropanol 4:1) showed that the reaction was complete. The slurry was cooled to 25°C and then granulated overnight. The slurry was filtered and the filter cake was washed with isopropanol (two times 90 mL). The wet cake was suspended in one liter of tetrahydrofuran (THF) and the resulting slurry was granulated at 25°C for 7 hours. The slurry was filtered, washed with THF (two times 100 mL), and then dried in vacuo at 42°C overnight. The title compound (54.4 g) was isolated as a tan solid (mp = 224-226°C with decomposition) in 90.2% yield. ^{13}C NMR (DMSO-d_6): δ 176.25, 166.33, 159.16, 143.28, 135.16, 131.84, 131.26, 129.64, 128.65, 126.88, 126.03, 125.21, 116.37, 109.58, 57.65, 51.58, 35.40, and 29.95. Dibenzyl disulfide was isolated as a reaction by-product from the mother liquors.

Example 2

1-[2-(6-Chloro-2,3-dihydro-2-oxo-1H-indol-5-yl)ethyl]-4-[imino(2-mercaptophenyl)methyl]piperazine dihydrochloride

The compound (5.0 g, 12.1 mmol) from Example 1 was suspended in 75 mL of THF at room temperature, and then 1.97 mL of concentrated hydrochloric acid was slowly added over 30 min affording a gummy solid. Water (5 mL) was added and the gummy solids were stirred for 6 hours to produce a finely divided solid which was granulated overnight. The mixture was filtered and the filter cake was washed with THF (10 mL). The product was dried in vacuo at 25°C overnight under a nitrogen bleed to give 5.87 g of the title dihydrochloride compound as a tan solid (mp = 232-240°C with decomposition). When the dihydrochloride was titrated with 0.2032 Molar sodium hydroxide, it showed pH equivalents points at 4.33 and 8.22 (pk_a = 3.1 and 5.5).

Preparation 1

3-(1-Piperazinyl)-1,2-benzisothiazole hydrochloride

Method A

Bis(2-cyanophenyl)disulfide (20.0 g, 74.5 mmol), anhydrous piperazine (64.2 g, 745 mmol), dimethyl sulfoxide (12.8 g, 164 mmol), and isopropanol (24 mL) were added to a 500 mL round bottom flask equipped with a mechanical

stirrer, thermometer, condenser topped with a nitrogen inlet and a connector leading to a bleach scrubber. After the flask was purged with nitrogen, the reactants were melted (at approximately 80°C) and then heated to reflux (110-126°C). After 24 hours at reflux, the reddish solution was sampled for thin-layer chromatography (elution with methylene chloride/isopropanol/triethylamine, 15:5:1) which showed that the reaction was complete. The solution was cooled to 85-90°C, at which point water (130 mL) was added. The resulting slurry was cooled to 30-35°C. The reaction mixture was then concentrated at reduced pressure (bp=50-60°C at 110 mm) to remove approximately 30 mL of distillate. The distillate was treated with bleach to destroy the dimethyl sulfide (DMS). Drager tubes (Drägerweck Ag Lübeck, Germany), which are selective for detecting ppm levels of dimethyl sulfide, showed that the reaction's headspace vapors contained less than 1 ppm residual DMS. A sample of the crude reaction mixture was analyzed by HPLC. The crude reaction mixture contained 3-(1-piperazinyl)-1,2-benzisothiazole (80%), 3,3'-(1,4-piperazinyl)-bis-1,2-benzisothiazole (4.6%), and 2-(1-piperazinyl)pyrazine (4%). After isopropanol (28 mL) and water (71 mL) were added, the slurry was cooled to 30°C, granulated for 0.5 hour, and then filtered through diatomaceous earth, e.g., Celite®, to remove 3,3'-(1,4-piperazinyl)-bis-1,2-benzisothiazole. The filter cake was washed with 56 mL of an isopropanol/water (1:1) solution. Toluene (170 mL) was added to the warm (32°C) filtrate, and then the separated aqueous layer was washed with fresh toluene (100 mL). The combined toluene layers were washed with water (100 mL) and then treated with decolorizing carbon, e.g., DARKO KB-B®, (2 g). The Celite® cake was rinsed with toluene (60 mL), and the combined wash and filtrate were concentrated at reduced pressure to 90 mL. Isopropanol (220 mL) was added to the concentrate and the yellowish solution was cooled to 20°C. The pH of the solution was slowly adjusted to 3.5-4.0 with 9.8 mL of concentrated hydrochloric acid. The resulting slurry was cooled to 0-5°C, granulated for 1 hour, and then filtered. The product cake was washed with cold isopropanol (80 mL), and then dried in vacuo at 40°C for 24 hours. The title compound (43.2 g) was isolated as a light yellow solid in 77.6% yield (98.5% hplc purity). The spectroscopic and physical properties of the solid were identical to an authentic sample (Caution: compound is a strong irritant). ^{1}H NMR (D_2O): δ 7.80 (m, 2H), 7.49 (m, 1H), 7.35 (m, 1H), 3.58 (m, 4H), and 3.42 (m, 4H).

^{13}C NMR (dimethyl sulfoxide): δ 162.72, 152.10, 128.15, 127.09, 124.63, 124.12, 121.21, 48.48, and 42.49.

Preparation 2

3-(1-Piperazinyl)-1,2-benzisothiazole • hydrochloride

Bis(2-cyanophenyl)disulfide (5.00g, 18.6 mmol), anhydrous piperazine (8.02g, 93.2 mmol), and isopropanol (5 mL) were combined under nitrogen and heated to reflux (115°C). The yellow solution was heated at reflux (110-115°C) for 23 hours and then cooled to 95°C. Water (30 mL) was added and the resulting suspension was cooled to 25°C and filtered. The filter cake was washed with 12 mL of water/isopropanol solution (2:1). Toluene (50 mL) was then added to the combined wash and filtrate. The toluene layer was separated and the aqueous layer extracted with additional toluene (25 mL). The combined toluene layers were washed with water (20 mL), treated with activated charcoal (DARCO KB-B®) (0.5g), filtered, and then concentrated at reduced pressure (42°C at 700 mm Hg) to 12 mL. Isopropanol (30 mL) was added to the concentrate and then the pH was adjusted to 4.4 with concentrated hydrochloric acid. The resulting slurry was cooled to 0 - 5°C, granulated for 1 hour, and then filtered. The product cake was washed with cold isopropanol (10 mL) and dried in vacuo at 42° C to give 3.22g (34% overall yield) of 3-(1-piperazinyl)-1,2-benzisothiazole. The product was a single spot by thin-layer chromatography.

The pH of the aqueous layer was adjusted to 4.0 with concentrated hydrochloric acid, and then extracted with methylene chloride (40 mL). The methylene chloride solution was concentrated at reduced pressure to an oil which was then dissolved in methanol (19 mL). The solution was cooled in an ice bath and 10% aqueous hydrogen peroxide solution (7 mL) was added with stirring. After stirring for 10 minutes, thin-layer chromatography showed that the reaction was complete. Water (12 mL) was added and the slurry was granulated for 1.5 hours. Product was filtered and dried in vacuo at 40°C to recover 1.64 grams (33% recovery) of bis(2-cyanophenyl)disulfide for recycle.

Preparation 3

3-(1-Piperazinyl)-1,2-benzisothiazole • hydrochloride

Anhydrous piperazine (49.4g, 0.57 mol) and t-butanol (10 mL) were added to a dry, 300 mL round bottom flask equipped with a mechanical stirrer, thermometer, condenser topped with a nitrogen inlet, and pressure-equalizing dropping tunnel. After the flask was purged with nitrogen, it was heated to 100°C in an oil bath. A solution of 3-chloro-1,2-benzisothiazole (19.45g, 0.11 mol) in t-butanol (10 mL) was added to the addition tunnel, and then slowly added to the reaction flask over 20 minutes to moderate an exothermic reaction (112 - 118°C). Once addition was complete the yellow solution was heated to reflux (121°C) and then maintained at reflux for 24 hours. Thin-layer chromatography showed that the reaction was complete. The reaction mixture was cooled to 85°C and 120 mL of water was added. The hazy solution was filtered and the filter cake rinsed with 60 mL of t-butanol/water (1:1) solution. The pH of the combined

filtrate and wash was adjusted to 12.2 with 50% aqueous caustic. The aqueous solution was extracted with toluene (200 mL), the layers were separated, and the aqueous layer was extracted with fresh toluene (100 mL). The combined toluene layers were washed with water (75 mL), and then the toluene solution was concentrated in vacuo at 48°C to 90 mL. Isopropanol (210 mL) was added to the concentrate and then the pH was slowly adjusted to 3.8 with 7.6 mL of concentrated hydrochloric acid. The resulting slurry was cooled to 0°C, granulated for 45 min, and then filtered. The filter cake was washed with cold isopropanol (50 mL) and then dried in vacuo at 40°C to afford 23.59g (80% yield) of 3-(1-piperazinyl)-1,2-benzisothiazole hydrochloride as an off white solid.

Preparation 4

3-(1-Piperazinyl)-1,2-benzisothiazole

3-(2-Cyanophenylthio)-1,2-benzisothiazole (0.25g, 0.93 mmol), anhydrous piperazine (0.80, 9.32 mmol), and isopropanol (0.25 mL) were added to a 6 mL round bottom flask equipped with a magnetic stirring bar, reflux condenser topped with a nitrogen inlet, and thermometer. The flask was purged with nitrogen and then immersed in a 120°C oil bath to give a yellow refluxing solution. After heating at 116-120°C for 25 hour, the reddish solution was cooled to 25°C and 5 mL of methanol was added. Thin-layer chromatography (methylene chloride/isopropanol/triethylamine, 15:5:1) showed that the reaction was essentially complete. The crude reaction solution was analyzed by high-pressure liquid chromatography to show that 3-(1-piperazinyl)-1,2-benzisothiazole was formed in 70% yield.

Preparation 5

3-(1-Piperazinyl)-1,2-benzisothiazole

Anhydrous piperazine (17.2g, 0.20 mol) and isopropanol (3.0 mL) were charged to a round bottom flask equipped with a mechanical stirrer, thermometer, condenser topped with a nitrogen inlet, and an addition tunnel. Once the flask was purged and then maintained under nitrogen, the mixture was heated to 90°C to afford a solution. A solution of 1-(2-cyanophenylthio)piperazine (4.38g, 20.0 mmol) in isopropanol (2.0 mL) was slowly added to the warm piperazine solution over 1 hour. Once the addition was complete, the solution was heated to reflux (118°C) for 24 hours. The reddish solution was cooled to room temperature and then analyzed by HPLC. 3-(1-Piperazinyl)-1,2-benzisothiazole was formed in 55% yield by HPLC assay.

Preparation 6

3-(2-Cyanophenylthio)-1,2-benzisothiazole

Method A

Bis(2-cyanophenyl)disulfide (1.25 g, 4.66 mmol), anhydrous piperazine (4.01 g, 46.6 mmol), and dimethyl sulfoxide (0.80 g, 10.3 mmol) in 15 mL of tetrahydrofuran were added to a 50 mL round bottom flask equipped with a magnetic stirring bar, thermometer, and condenser topped with a nitrogen inlet. After the flask was purged with nitrogen, the mixture was heated at reflux (75°C) for 25 hours. The reaction mixture was cooled to 25°C, and the tetrahydrofuran was removed at reduced pressure. The resulting solid was dissolved in a 40 mL of a methylene chloride/water (1:1) mixture, the layers were separated, and the organic layer washed with water (20 mL). The methylene chloride solution was evaporated to afford a crude solid (0.85 g) which was crystallized from isopropanol (17 mL) to give light yellow crystals. After filtration, the product was dried in vacuo at 40°C to give 0.39 g (31% yield) of 3-(2-cyanophenylthio)-1,2-benzisothiazole. Melting point 115.5-117°C. ^{1}H NMR ($CDCl_3$): δ 8.03 (m, 1H), 7.92 (m, 1H), 7.77 (m, 1H), 7.70 (m, 1H), 7.57 (m, 2H), and 7.48 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 154.99, 152.30, 134.83, 134.56, 134.06, 133.24, 129.07, 128.51, 125.33, 123.29, 120.13, 117.13, and 116.95. Analytical calculated for $C_{14}H_8N_2S_2$ C, 62.66; H, 3.00; N, 10.44; S, 23.90. Found: C, 62.43; H, 3.01; N, 10.68; S, 24.05. A X-ray crystal structure was also obtained to confirm structure.

Preparation 7

3-(2-Cyanophenylthio)-1,2-benzisothiazole

Method B

Bis(2-cyanophenyl)disulfide (0.40 g, 1.48 mmol) and 2-merceptobenzonitrile (0.20 g, 1.48 mmol) were combined in 2 mL of isopropanol and were heated at reflux (90°C) for 25 hours under a nitrogen (N_2) atmosphere. 3-(2-Cyanophe-

nylthio)-1,2-benzisothiazole was formed in 69% yield by HPLC assay.

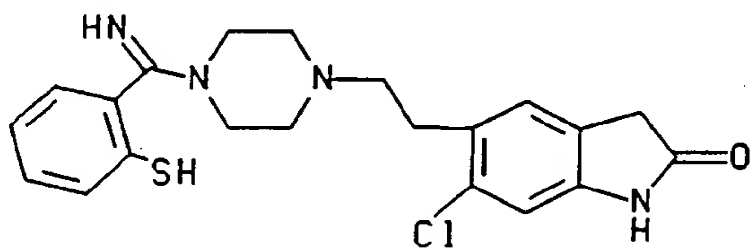
Preparation 8

1-(2-Cyanophenylthio)piperazine

Anhydrous piperazine (22.5g, 261 mmol) and tetrahydrofuran (100 mL) were combined under a nitrogen atmosphere and then heated to 60-65°C. 3-Chloro-1,2-benzisothiazole (10.0g, 59.0 mmol) was slowly added over one hour to the warm piperazine solution and then the resulting reddish solution was heated at 65°C for 17 hours. Thin-layer chromatography (ethyl acetate/hexanes/triethylamine, 10:10:1) showed that the reaction was complete. The mixture was cooled to room temperature and then filtered. After toluene (100 mL) was added, the solution was concentrated at reduced pressure (40°C) to one-half volume. The toluene solution was washed with water (100 mL), and the aqueous layer was extracted with fresh toluene (25 mL). The combined toluene layers were concentrated at reduced pressure to about 30 mL. After cooling the solution to 0-5°C, hexanes (50 mL) was slowly added. The resulting crystals were granulated for 1 hour at 0 to 5°C, filtered, and the cake was washed with fresh hexanes (15 mL). After drying the solids for 18 hours at 23°C, 11.51 grams (89% yield) of a yellow crystalline solid (m.p. = 67-71°C) was isolated. The crude sulfenamide contained approximately 5% of 1,4-bis(2-cyanophenylthio)piperazine by NMR analysis. Title sulfenamide was stored at 0 to -10°C to prevent slow conversion to 1,4-bis(2-cyanophenylthio)piperazine with heating or storage at room temperature. ^{1}H NMR ($CDCl_3$): δ 7.63 (m,1H), 7.56 (m, 3H), 7.21 (m, 1H), 2.96 (m, 4H), and 2.87 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 142.69, 133.55, 132.67, 128.14, 126.69, 116.80, 110.24, 57.34, and 47.06. HRMS Found: 220.0878; $C_{11}H_{13}N_3S$ Requires (FAB P+1): 220.0908

Claims

1. A compound of the formula



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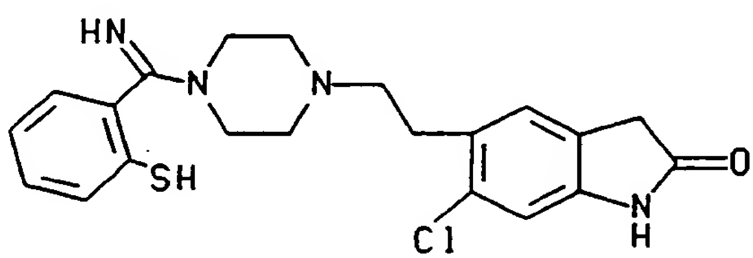
or a pharmaceutically acceptable salt thereof.

2. A process for preparing a compound of the formula



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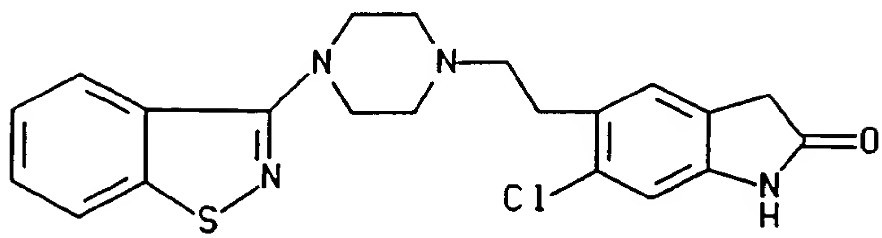
comprising, reacting a compound of the formula



II

with a reducing agent.

3. A process according to claim 2 wherein said reducing agent is benzyl mercaptan.

4. A process according to claim 3 wherein said reducing agent benzyl mercaptan comprises 2.2 equivalents relative to the amount of ziprasidone.

5. A process for according to claim 4 wherein said reaction is performed in the presence of a solvent.

6. A process according to claim 5 wherein said solvent is isopropanol.

7. A process according to claim 6 wherein said reaction is run at about 85°C for about 6 hours.

8. A pharmaceutical composition having neuroleptic activity comprising the compound according to claim 1 in an amount effective in the treatment of neuroleptic diseases, and a pharmaceutically acceptable carrier.

9. A method of treating neuroleptic diseases which comprises administering to a subject in need of such treatment a neuroleptic amount of the compound according to claim 1.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 97 20 0175

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
D,A	US 4 831 031 A (LOWE III JOHN A ET AL) 16 May 1989 * the whole document *	1-9	C07D209/34 A61K31/40 C07D417/12
A	EP 0 388 081 A (SANTEN PHARMA CO LTD) 19 September 1990 * the whole document *	1-9	
A	WO 90 02552 A (PFIZER) 22 March 1990 * the whole document *	1-9	
A	CHEMICAL ABSTRACTS, vol. 96, no. 13, 29 March 1982 Columbus, Ohio, US; abstract no. 103785w, BOESHAGEN ET AL.: "Reduction of 3-amino-1,2-benzothiazoles and ..." XP002031708 & Liebigs Ann. Chem., 1982, (1), 14-27 * abstract *	1-9	
A	CHEMICAL ABSTRACTS, vol. 124, no. 15, 9 April 1996 Columbus, Ohio, US; abstract no. 202220m, BRIEADDY ET AL.: "The synthesis of cis-6,12-diaryl-6H,12H-dibenzo[b,f]dithiocin-6,12-imine and ..." XP002031709 & J. Heterocycl. Chem., 1995, 32(6), 1683-1686 * abstract *	1-9	TECHNICAL FIELDS SEARCHED (Int.Cl.6) C07D A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
MUNICH	28 May 1997	Steendijk, M.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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A : technological background
O : non-written disclosure
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T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
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